

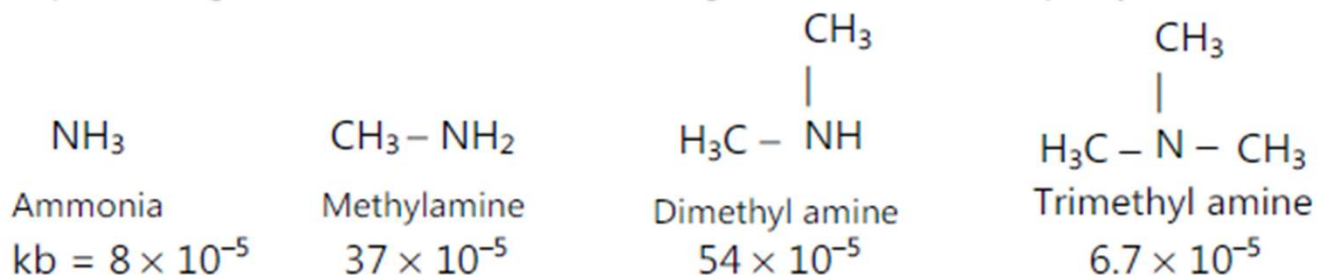
**PHARMACEUTICAL ORGANIC CHEMISTRY-II**  
**SECOND YEAR B. PHARMACY**  
**(SEMESTER-III)**  
**AROMATIC AMINES**



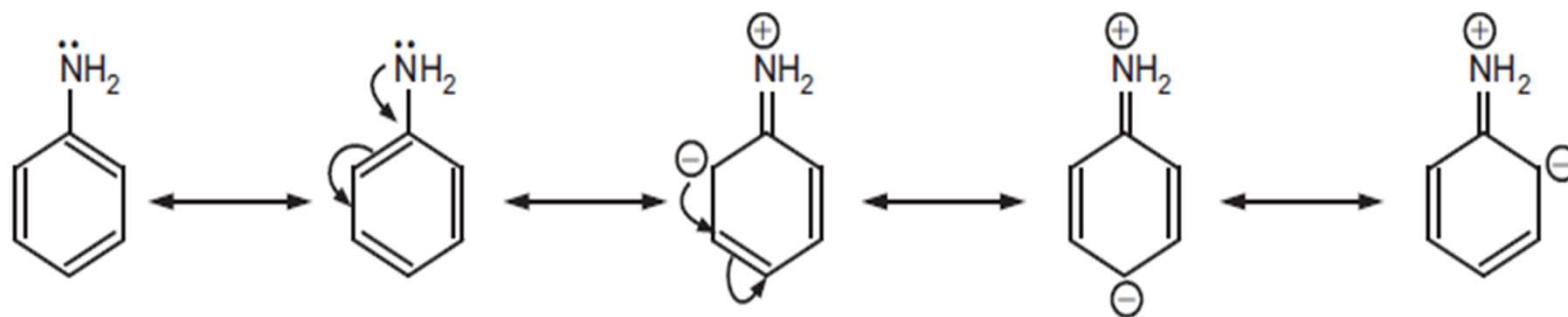
**By Prof. D. K. Kadam**  
**K. K. Wagh College of Pharmacy, Nashik**

## BASICITY OF AMINES

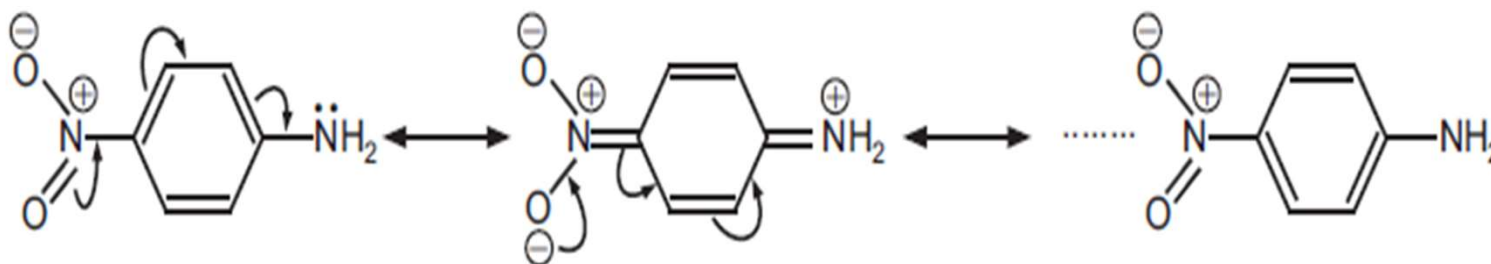
- Amines are basic in nature. The presence of lone pair of electron on nitrogen atom of the amine makes it basic. This lone pair of electrons is available for the formation of a new bond with a proton or Lewis acid.
- Aliphatic amines are stronger bases than ammonia. This is because the alkyl groups are electron releasing. They increase the electron density around the nitrogen, thereby increasing the availability of the lone pair of electrons. The greater the number of electron releasing alkyl groups, stronger the base. Also the nitrogen is bonded to  $sp^3$  hybridised carbon atom.



- However, in aniline, the nitrogen atom is again bonded to  $sp_2$  hybridized carbon atom (which is electronegative) but, more significantly, the unused electron pair on nitrogen can interact with the delocalized p ( $\pi$ ) orbitals of the aromatic ring. Aniline is a weaker base than primary aliphatic amines and this may be explained by resonance.

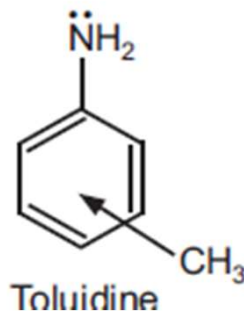


- Aniline molecule is thus, stabilized w.r.t. the anilinium cation and it is therefore “energetically unprofitable” for aniline to take up a proton. Hence, methylamine is more basic than ammonia and aniline is a weaker base than methylamine.
- The low basicity of aromatic amines is thus due to the fact that, the amine is stabilized by resonance to a greater extent than is the ion.
- Aniline is a weaker base than ammonia because the lone pair of electrons is partly shared with the ring and is thus less available for sharing with a hydrogen ion. The tendency for the  $-NH_2$  group to release electrons to the aromatic ring makes the ring more reactive towards electrophilic attack, at the same time this tendency necessarily makes the amine less basic.
- The effect of a ring substituent on basicity depends on whether the substituent is electron attracting or releasing, its ability to enter into resonance with the amino-group and its position. Example: All the nitroanilines are weaker bases than aniline.

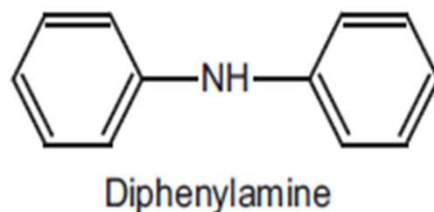


- The nitro group has a strong  $-I$  effect. This tends to draw into the ring the lone pair on the N atom of the  $NH_2$  group, with consequent decrease in basicity.

- **Toluidine is more basic than aniline.** In o and p-toluidine the  $\text{CH}_3$  group is electron donating and increases the electron density on N atom, making the electrons available for protonation more than in aniline.

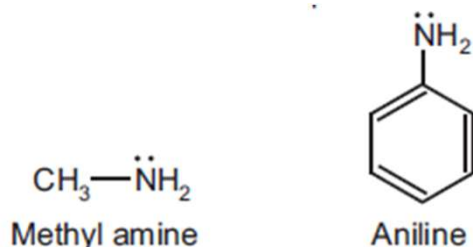


- **Diphenylamine is a weaker base than aniline:** This is because it contains two negative phenyl groups instead of one. The non-bonding electron pair of N is now even less available as it gets distributed over two phenyl groups.

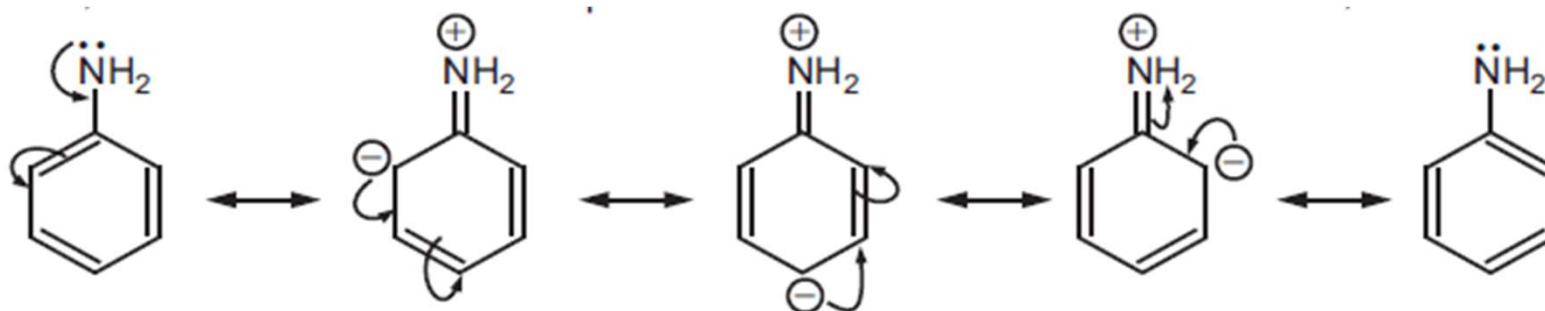


# EFFECTS OF SUBSTITUTENTS ON BASICITY OF AMINES

- Methylamine is stronger base than aniline in aqueous medium.



- The nitrogen atom of methylamine is  $sp_3$  hybridized and in aniline it is  $sp_2$  hybridized, but both of them hold the same number of H atoms. The + I effect of  $-\text{CH}_3$  group in methylamine makes it strong base. But in aniline, there is strong delocalization effect instead of + I effect, this makes the electron pair less available for donation. Hence, it is a weak base.



- An electron releasing substituents like  $-CH_3$ ,  $-NH_2$ ,  $-OCH_3$  group increases the basicity of aniline and an electron withdrawing substituents like  $-X$ ,  $-NO_2$ ,  $-SO_3$ ,  $-COOH$  decreases the basicity. Electron release tends to disperse the positive charge of the anilinium ion and thus stabilizes the ion relative to the amine.
- Electron withdrawal tends to intensify the positive charge of the anilinium ion and thus destabilizes the ion relative to the amine.
- From another point of view, we can consider that an electron releasing group pushes electrons toward nitrogen and makes the fourth pair more available for sharing with an acid, whereas an electron withdrawing group helps pull electrons away from nitrogen and thus makes the fourth pair less available for sharing.

## **FACTORS AFFECTING ON BASICITY**

The following factors governs the basicity of aromatic amines:

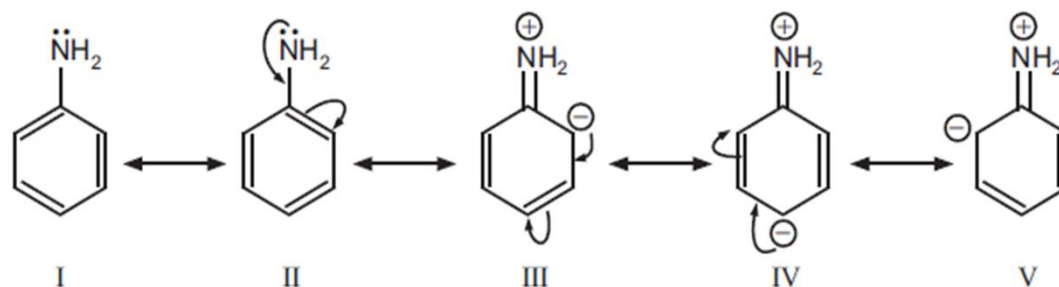
1. Resonance effect
2. Inductive effect
3. Hydrogen bonding
4. Orbital nature of electron pair
5. Steric effect
6. Solvation effect
7. Electronegativity of bonded atoms



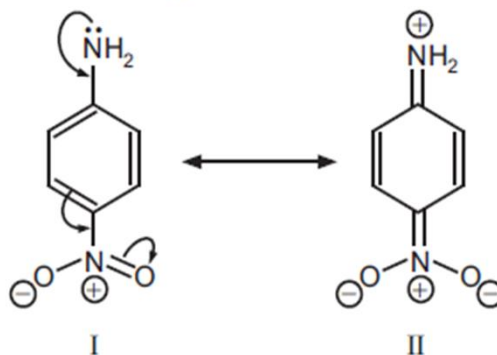
# 1. Resonance Effect

The more the number of contributing structures in a resonance hybrid of a neutral or negatively charged species, the more is the stability and greater is delocalization of electrons. The greater the delocalization, the lower is the probability of donating electron pair. Therefore, as resonance stabilization, i.e., delocalization increases, basicity decreases.

Example: Aniline is stronger base than *p*-nitroaniline, as aniline contributes 5 resonating structures whereas *p*-nitroaniline is contributing only 2 structures.



Resonating structures of aniline



Resonating structures of *p*-nitroaniline

## 2. Inductive Effect

The +I effect increases the availability of electrons on a particular atom and thus increases the basicity but decreases acidity. A **greater + I effect means greater basicity and lower acidity.**

For example, the substituents on aniline *viz. alkyl group like*  $R_3C$ ,  $R_2CH$ ,  $RCH_2$ ,  $CH_3$  increase basicity.

The – I effect decreases the electron density on particular atom and hence decreases the basicity but increases acidity. The **higher – I effect, the lower is basicity.**

For example: substituents like  $NR_3^+$ ,  $NH_3^+$ ,  $NO_2$ ,  $CN$ ,  $COOH$ ,  $SO_3H$  etc. decrease basicity.

### 3. Hydrogen Bonding

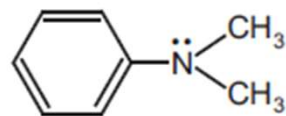
- Hydrogen bonding stabilizes the base and **decreases its basicity.**

### 4. Orbital Nature of Electron Pair

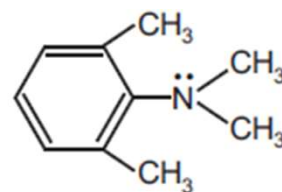
- As the s-character of an orbital increases, the attractive force between the electron pair and the nucleus increases; this means the availability of electron pair for donation decreases, *i.e., basicity decreases and acidity increases.*

## 5. Steric Effect

- The steric hindrance **decreases basicity**. e.g. *N,N*-dimethylaniline is more basic than *N,N*,2,6-tetramethylaniline.

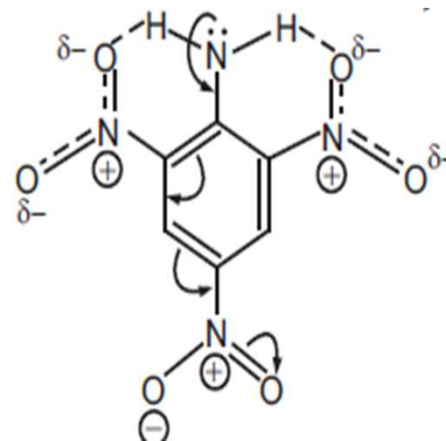
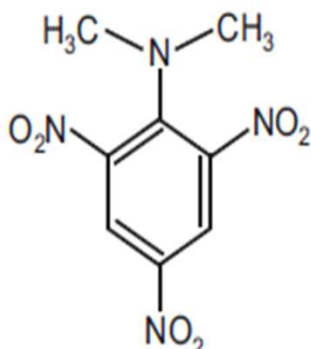


*N,N*-Dimethylaniline



*N,N*,2,6-Tetramethylaniline

- Steric hindrance inhibits delocalisation of electrons and thus electrons are readily available for donation. This is possible in *N,N*,2,6-tetramethylaniline, where steric hindrance takes place and this is found to be six times weaker basic than *N,N*-dimethylaniline.



- The strong steric inhibition of resonance in 2, 4, 6-trinitro-*N,N*-dimethylaniline attributes to the ready availability of electrons of the NH<sub>2</sub> group, while in 2, 4, 6-trinitroaniline, strong internal H-bonding with nitro groups at 2 and 6 positions makes the molecules planar and thus help to delocalize the lone pair of electrons of NH<sub>2</sub> group.

## 6. Solvation Effect

Solvation effect helps to stabilize a species. A greater stability means a lower reactivity. Thus, when a base gets stabilized by solvation, the availability of electron decreases and hence its basicity will be lower than expectation.

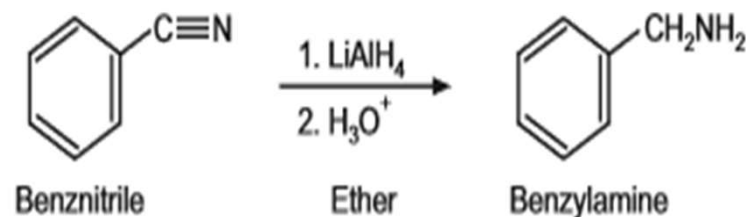
**Example: Dimethylamine is more basic than trimethylamine in aqueous solution whereas vice-versa is chlorobenzene medium. The hydration effect stabilises dimethylammonium ion in aqueous medium and makes more basic than trimethylamine, whereas trimethyl ammonium ion gets stabilized in chlorobenzene medium due to + I effect of  $-CH_3$  group.**

## 7. Electronegativity of Bonded Atoms

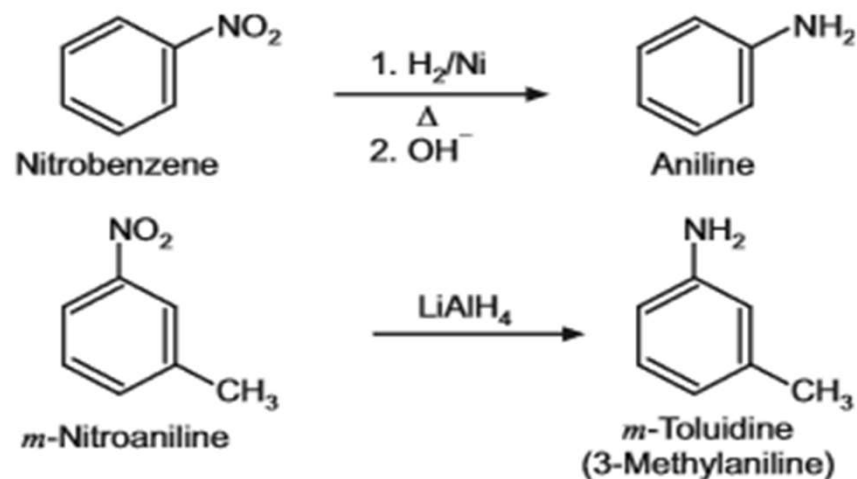
- The greater the electronegativity of atom holding donatable electrons, lower is the basicity.

## METHOD OF PREPARATION OF AROMATIC AMINES.

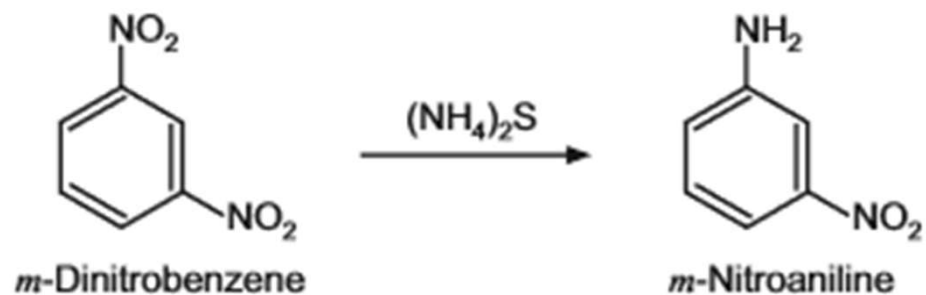
- Reduction of Nitriles-** Nitriles can be reduced by lithium aluminium hydride ( $\text{LiAlH}_4$ ) to primary amines.



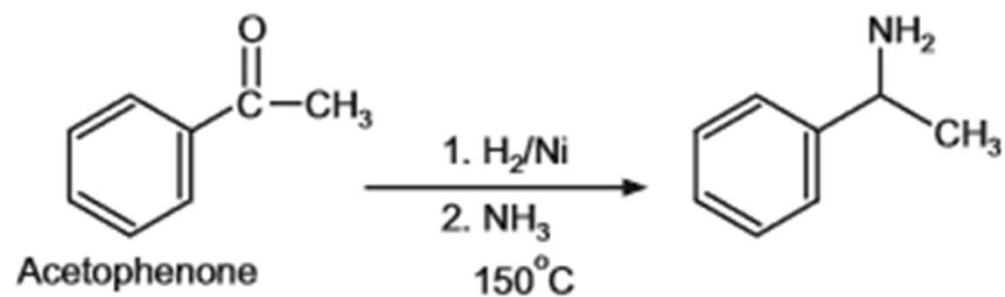
- Reduction of Nitrocompounds-** Aromatic amines are normally prepared by reduction of the corresponding aromatic nitro compound.



### 3 .Selective Reduction by Ammonium Sulphide

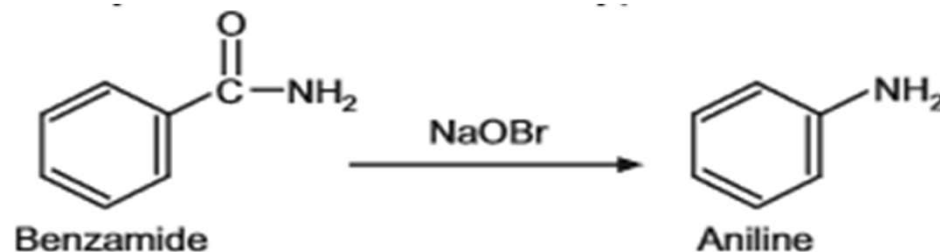


### 4. Reductive Amination of Ketone

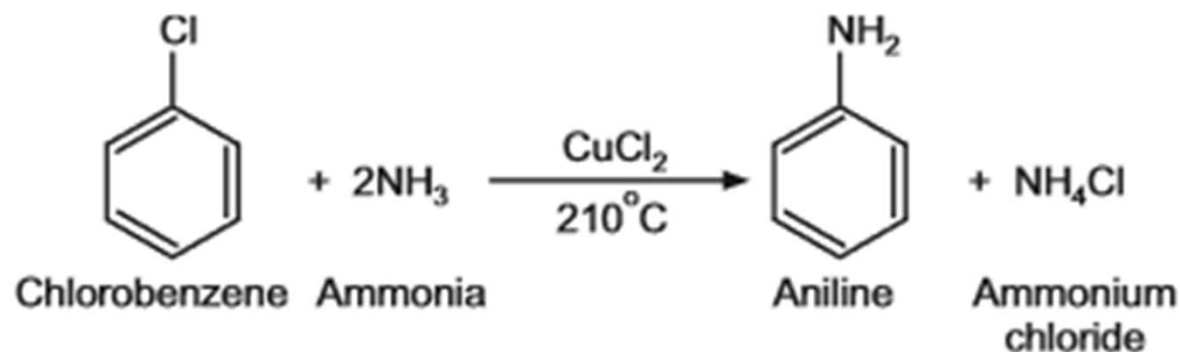




**5. Hoffmann Rearrangement** It yields primary amine. It involves conversion of an aromatic amide to primary amine with one carbon atom less by the action of sodium hypobromite.

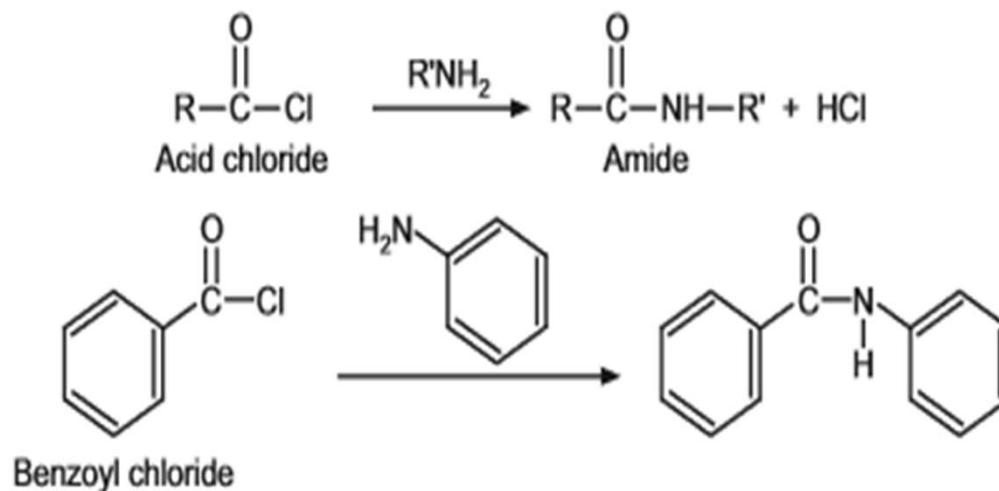


**6. Ammonolysis of Aryl Chloride** Aryl chlorides when heated at high temperature and pressure with ammonia and copper salt yield primary aromatic amines

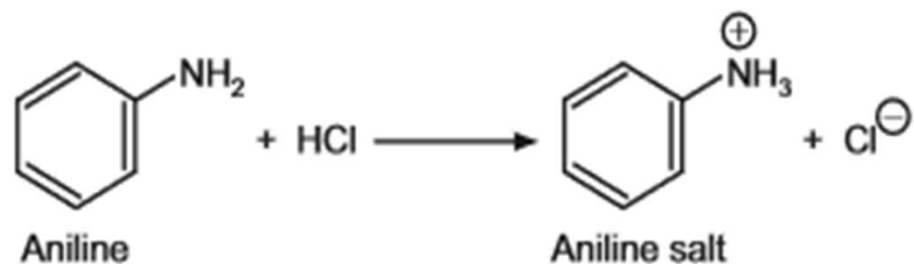


# REACTIONS OF AROMATIC AMINES.

**1. Formation of Amide from Acyl Chloride** - Addition of 1°, 2° amines to acid chloride results in formation of amide.

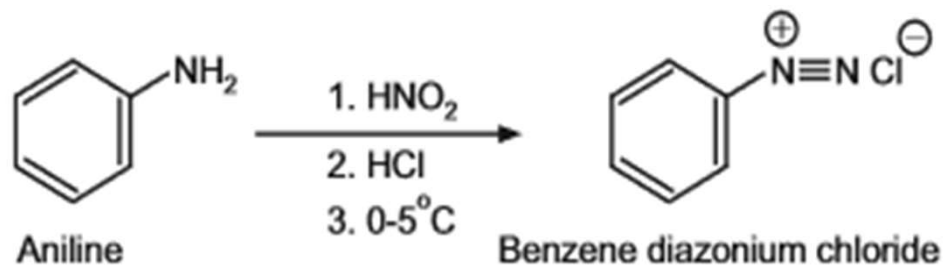


**2. Salt Formation** - Reaction of amines with acid will give amine salt.

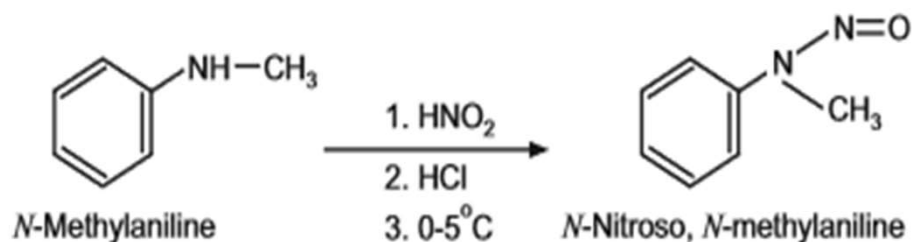


### 3. Reaction with Nitrous Acid

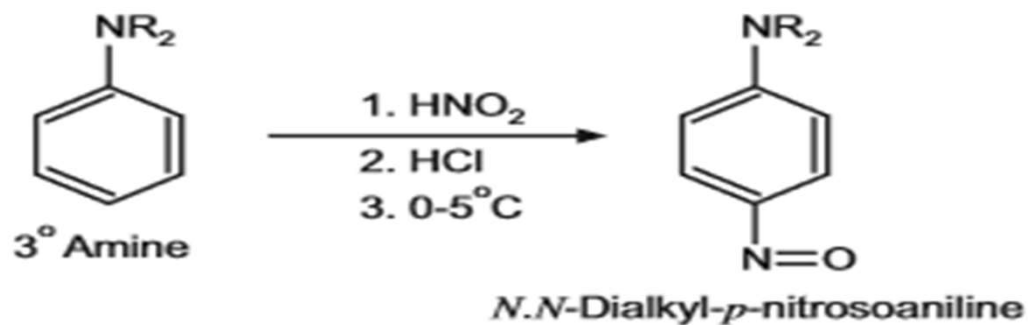
(a) Primary aromatic amine form diazonium salt at 0°C with nitrous acid.



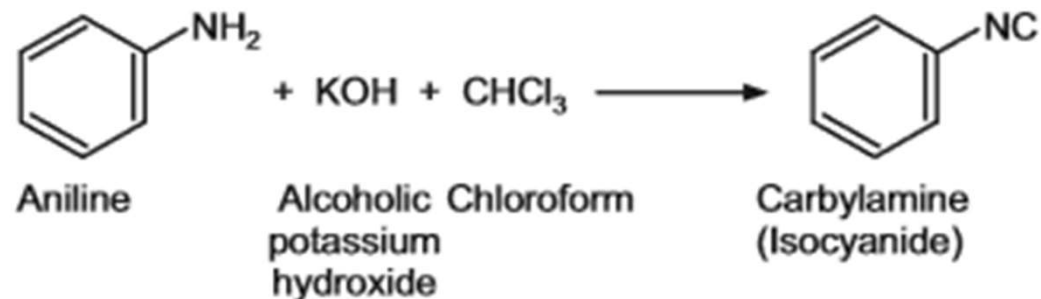
(b) Secondary aromatic amines form nitrosoamine with nitrous acid. (N-nitrosation)



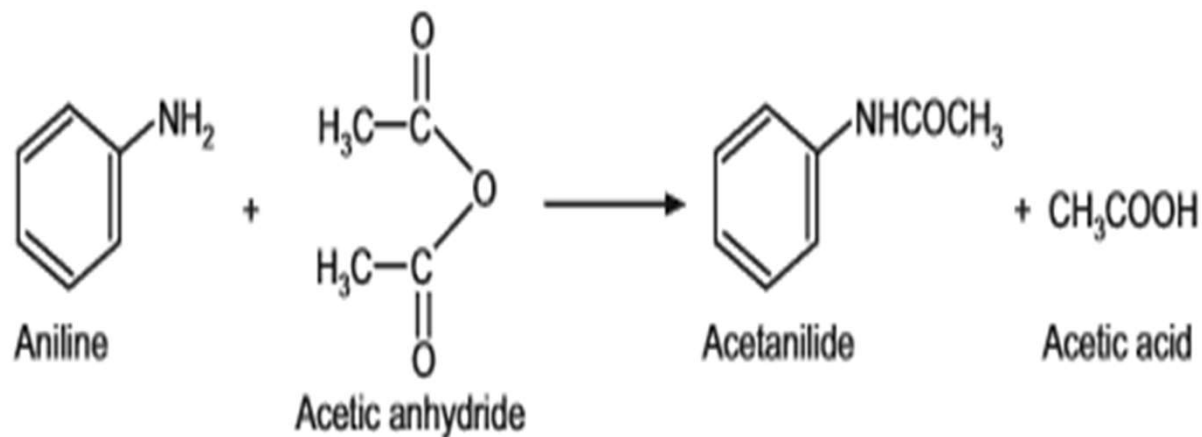
(c) Tertiary amines react with nitrous acid to form *N,N*-nitrosoammonium compounds (C-nitrosation).



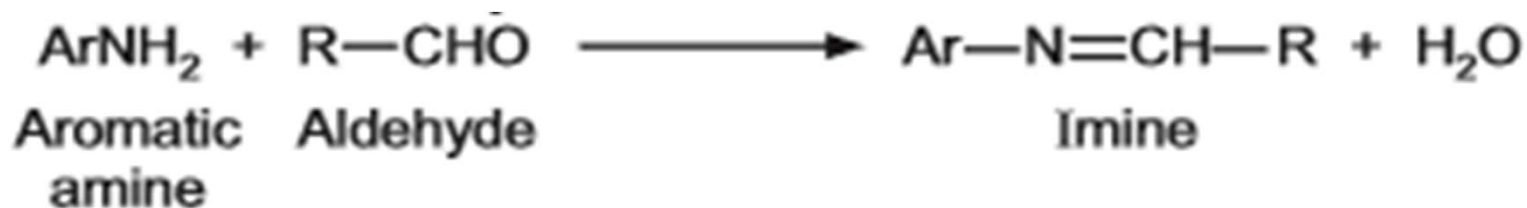
**4. Carbylamine Reaction-** Primary aromatic amines react with ethanolic KOH and chloroform to form carbylamines or isonitriles/isocyanides, which have a disagreeable odour.



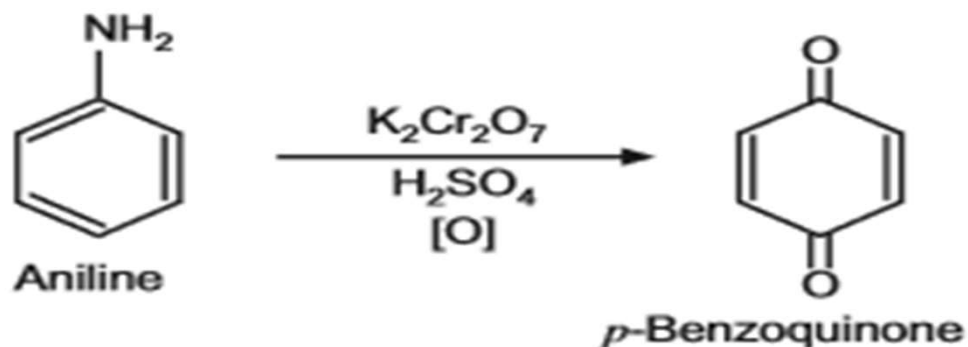
**5. Acetylation-** Primary aromatic amines react with acid halides or anhydrides to form anilides.



**5. Reaction with Aldehydes (Schiff's Base)** - Aromatic amines react with aldehydes to form imines (Schiff's bases).



**6. Oxidation Reactions** - Aromatic amines are readily oxidized to give products depending on conditions. Example: Aniline on oxidation with  $\text{K}_2\text{Cr}_2\text{O}_7$  and  $\text{H}_2\text{SO}_4$  gives *p*-benzoquinone.



# ARYL DIAZONIUM SALTS

## History of Aryl Diazonium Salts

The chemistry of diazonium salts has been studied for long starting around 1858. Several name reactions associated with aryl diazonium salts including the **Sandmeyer reaction (1884)**, the **Pschorr cyclization (1896)**, the **Gomberg–Bachman** are well documented in the literature.

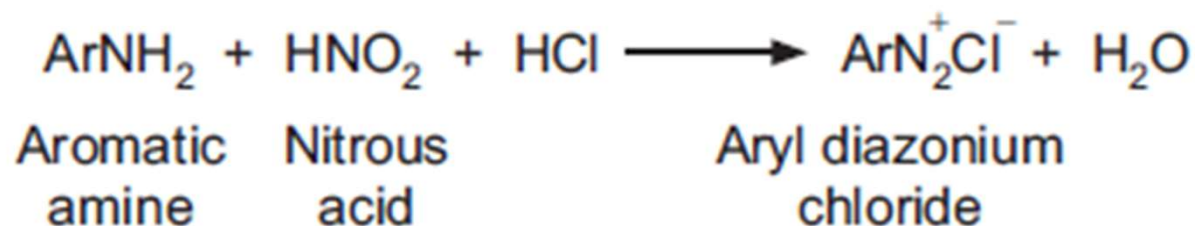
In **1884, Sandmeyer disclosed** that by treatment with copper(I) chloride, benzene diazonium salt was converted into **chlorobenzene**. He also showed that **bromobenzene** could be formed by using copper(I) bromide, and **benzonitrile** was obtained when **copper(I) cyanide** was used. 12 years later, **Pschorr reported a method for the preparation of biaryltricyclics** by intramolecular substitution of one arene with an aryl radical, which is generated *in-situ* from an aryl diazonium salt by copper catalysis.

In **1924, Gomberg and Bachmann developed an intermolecular version of Pschorr's** radical biaryl synthesis, which is now known as the Gomberg–Bachmann reaction. Only three years later, an important breakthrough was achieved by **Balz and Schiemann**, who reported thermal decomposition of aromatic diazonium tetrafluoroborates. The reaction leads to the formation of **aromatic fluorides, which cannot be accessed by the Sandmeyer reaction**.

In **1939, Meerwein and co-workers reported an extensive study on the reaction of aromatic diazonium salts with  $\alpha,\beta$ -unsaturated carbonyl compounds**. The reaction was later known as **Meerwein arylation, in which the aryl group adds across the double bond**.

## Aryl Diazonium Salts

- Primary aromatic amine is treated with nitrous acid in a well cooled solution to give unstable compound known as **diazonium salt**.

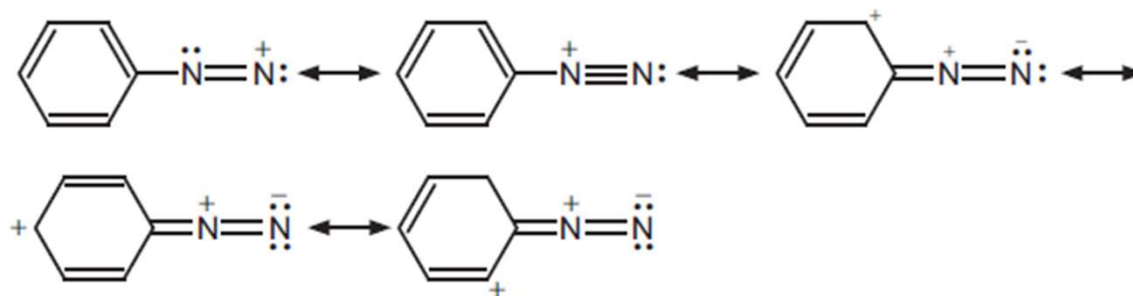


- The formation of diazonium compound by the interaction of sodium nitrite and primary aromatic amine in an ice-cold solution is known as diazotization.

Diazonium salt has the structure  $[\text{Ar}-\text{N}^{\equiv}\text{N}]^+ \text{X}^-$ .

It is a colourless solid, extremely soluble in water and forms complex with many metallic salts, like zinc chloride,  $(\text{ArN}_2)_2^{2+}$ ,  $\text{ZnCl}_4^{2-}$ . This complex salt is stable in water.

The stability of aryldiazonium salts relative to alkyldiazonium salts ( $\text{RN}_2^+ \text{X}^-$ ) is also due to resonance involving benzene ring.



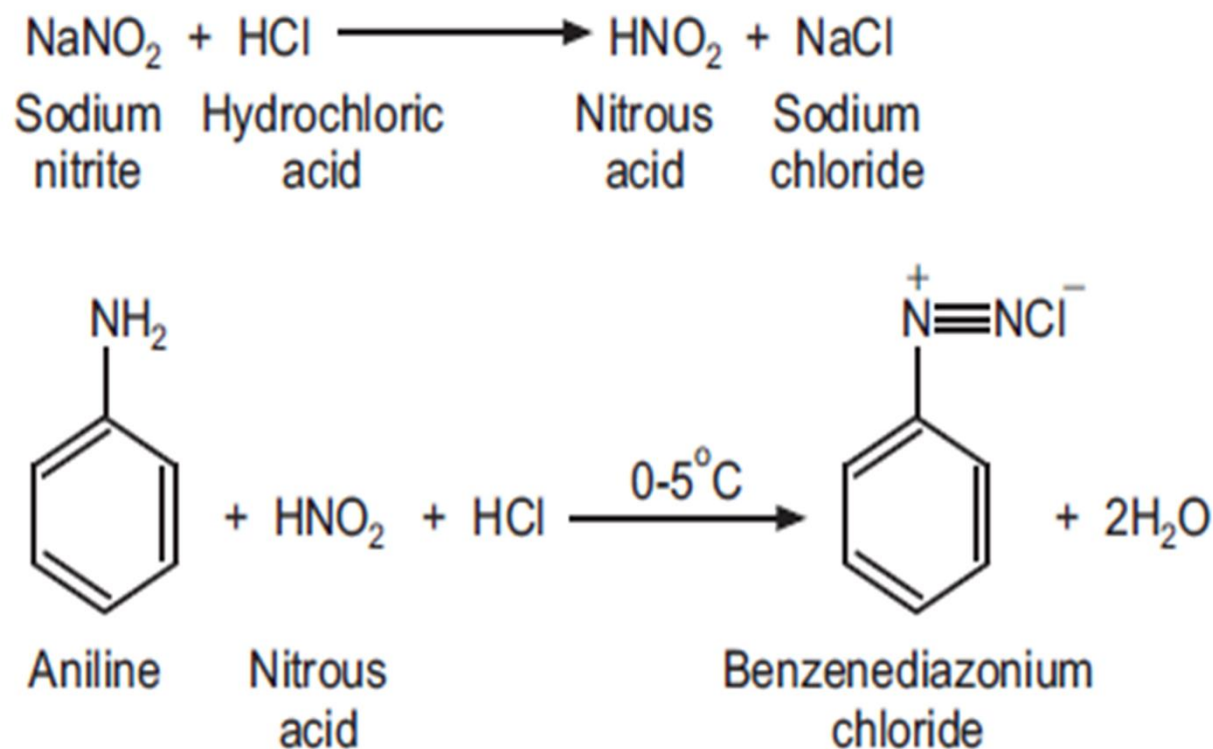
**Resonance structures of Benzenediazonium cation**

The diazonium salts are very important synthetic reagents, being the starting point in the preparation of various aromatic compounds, dyes and drugs.



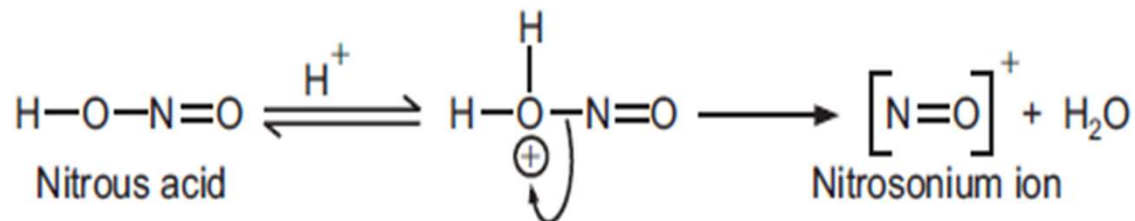
## PREPARATION OF BENZENE DIAZONIUM CHLORIDE

- It is prepared by treating a solution of aniline in dilute HCl with sodium nitrite ( $\text{NaNO}_2$ ) solution at  $0-5^\circ\text{C}$ . Sodium nitrite reacts with HCl to produce nitrous acid. The nitrous acid then reacts with aniline to give the diazonium salt.

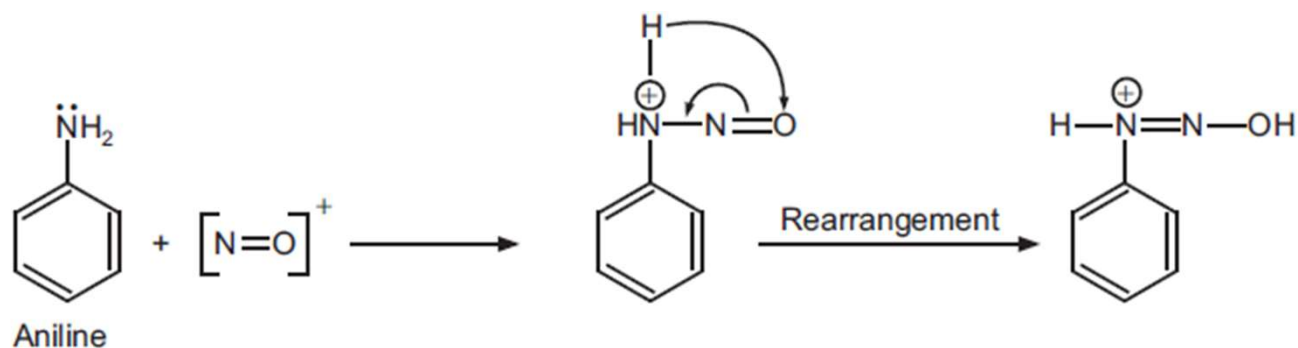


## ○ Mechanism:

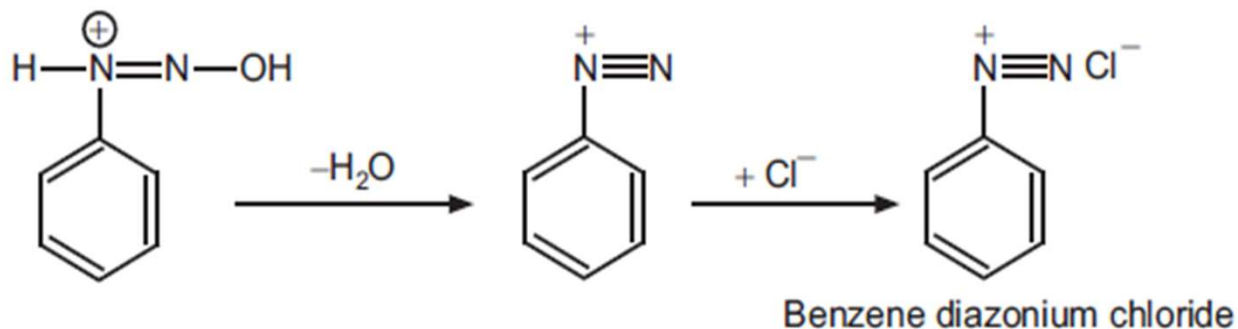
Step 1 : Formation of nitrosonium ion from nitrous acid.



Step 2 : Nitrosonium ion combines with aniline to form nitrosoaniline.



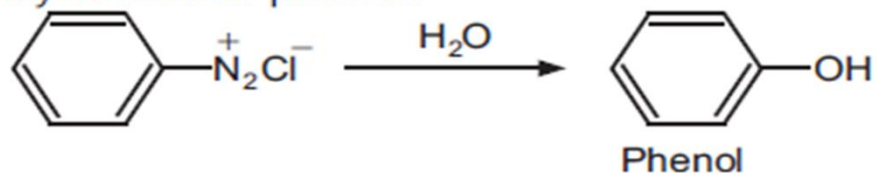
Step 3 : Dehydration to form diazonium ion which takes up Cl<sup>-</sup> to yield diazonium salt.



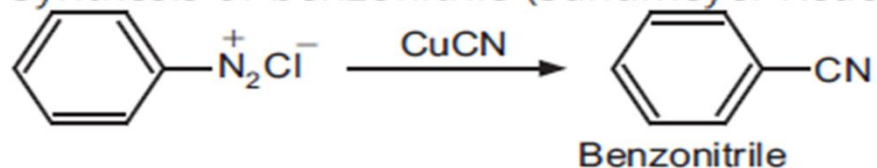
# SYNTHETIC APPLICATIONS OF ARYL DIAZONIUM SALTS

- These reactions are mostly the nucleophilic displacement reactions of the diazonium group by nucleophiles like  $\text{OH}^-$ ,  $\text{CN}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{F}^-$ ,  $\text{H}^-$ ,  $3\text{H}^-$ ,  $\text{OCH}_3^-$  etc.

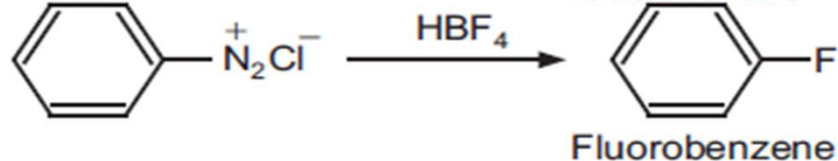
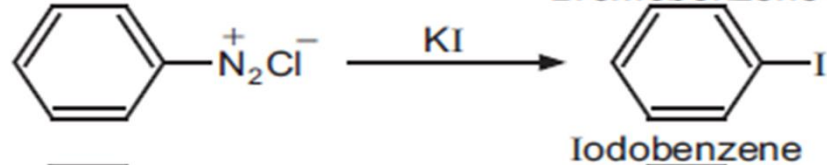
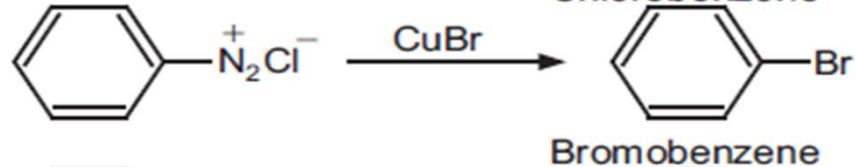
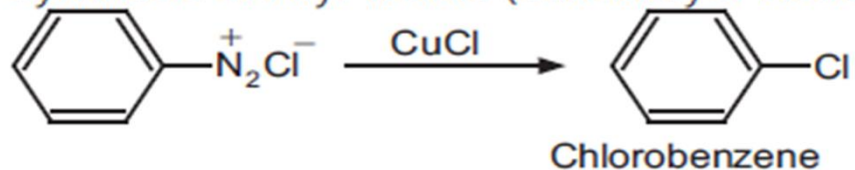
## 1. Synthesis of phenol.



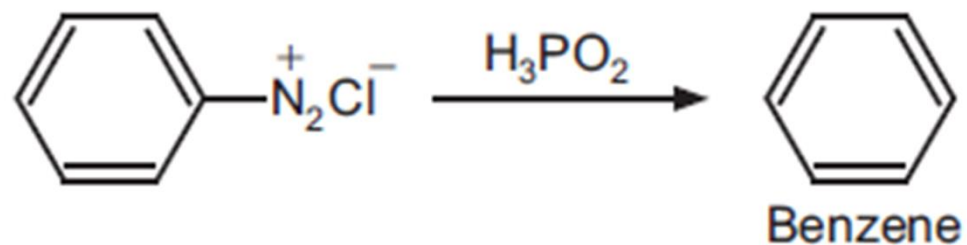
## 2. Synthesis of benzonitrile (Sandmeyer Reaction)



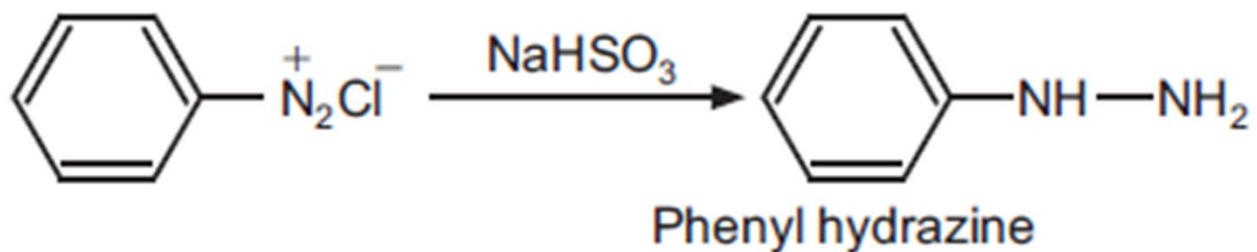
## 3. Synthesis of Aryl-halide (Sandmeyer Reaction)



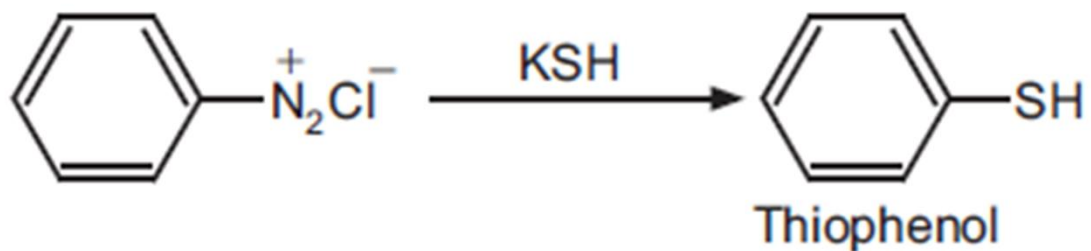
#### 4. Synthesis of Arenes



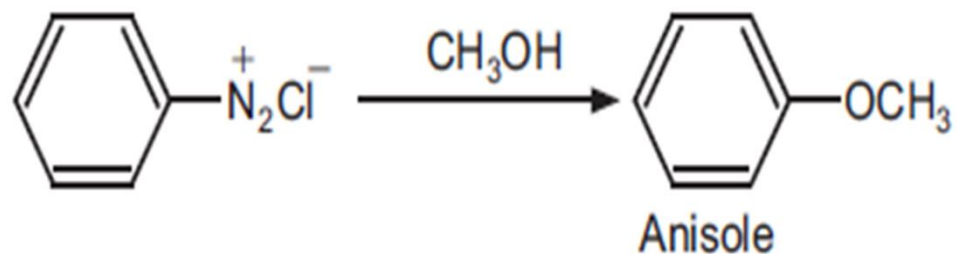
#### 5. Synthesis of Phenylhydrazine



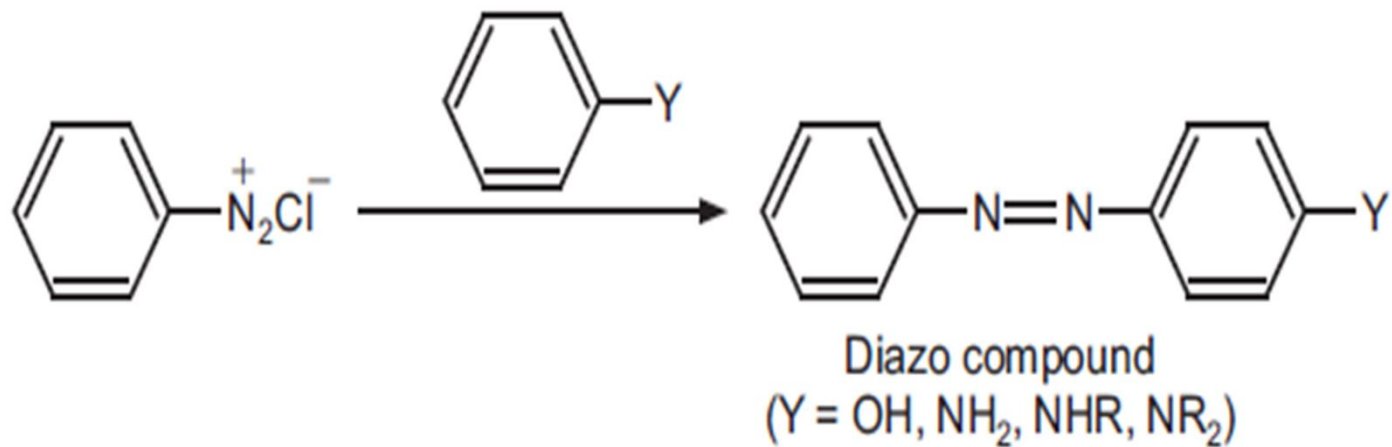
#### 6. Synthesis of Thiophenols (Leuckart thiophenol reaction)



## 7. Synthesis of Anisole



## 8. Diazo-coupling Reactions



## IMPORTANCE OF DIAZONIUM SALTS

- (i) Arene diazonium salts are common, easily prepared and highly useful intermediates in organic synthesis due to their rich reactivity and diverse transformations.
- (ii) In addition, aryl diazonium salts serve as an alternative to aryl halides, which have been widely used in transition metal mediated cross coupling reactions for carbon carbon and carbon-hetero bond formation.
- (iii) They find application in the dye and pigment industries and are used to produce dyed fabrics.
- (iv) Due to their property of breaking down near the ultraviolet light, they are used in document reproduction.
- (v) They are useful in the synthesis of a large variety of organic compounds, especially aryl derivatives.
- (vi) It is not possible to prepare substituted aromatic compounds by direct substitution in benzene. For these compounds, we use replacement of diazo group in diazonium salts.
- (vii) They are used as intermediates for introducing  $-F$ ,  $-Br$ ,  $-Cl$ ,  $-I$ ,  $-NO_2$ ,  $-OH$  and  $-CN$  groups into the aromatic ring.